UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR No.: 0054358
Date: September 20, 2006

MEMORANDUM

SUBJECT: CLODINAFOP-PROPARGYL: HED's Response to Syngenta's Comments Regarding MRID 46012925 (August 1, 2006). PC Code 125203; DP Number 332661.

FROM: Jess Rowland, Co-Chair
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Health Effects Division (7509P)

TO: Paula Deschamp, Chief
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and

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CONCLUSION: The brain morphometric changes observed in the PND 63 females at the high dose are treatment-related and are not "judged to be incidental to treatment" as noted by the Registrant. Therefore, level 4 corpus callosum thickness data from the mid- and the low-dose groups are required. Additionally, the other brain morphometric measurements in which statistical significant differences were seen should also be evaluated in male and female mid- and low-dose groups, for both PNDs 12 and 63.

I. BACKGROUND

The Health Effects Division (HED), following review of a Developmental Neurotoxicity (DNT) Study conducted with clodinafop-propargyl (MRID No. 46012925; TXR No. 0052183), which was sponsored by Syngenta and conducted by Central Toxicology Laboratory (CTL) in England, concluded that the 24% increase in the level 4 corpus callosum thickness at the high dose (500 ppm) is treatment-related and requested this data for the mid- and low-doses.

The Registrant, in their response, questioned the above conclusion and determined that values seen for the high-dose females represent normal variation in this parameter (*sic* corpus callosum) for animals of this age (PND 63) and strain (Wistar-derived Alpk:AP) and that the statistically significant difference is incidental to treatment. To support their conclusion, the Registrant provided a table listing the mean ± SD and the range of the corpus callosum thickness values for thirteen chemicals, clodinafop-propargyl inclusive, for which DNT studies were conducted using the Alpk:AP strain of Wistar rats at CTL in England (Email with attachment from Tom Parshley, Syngenta, to James Stone, EPA; August 1, 2006).

II. EVALUATION OF SYNGENTA'S RESPONSE

The DNT Workgroup, along with Karl Jensen of EPA's Office of Research and Development, met on August 23, 2006 to re-examine findings concerning the clodinafop-propargyl DNT. Specifically, the Workgroup examined the rationale submitted by Syngenta explaining why brain morphometrics data from mid- and low-dose groups were not processed and measured for certain brain regions where significant effects were observed in the high-dose group, compared to controls. Previously, the Workgroup found that, "The changes in morphometric measurement in the brain including a large (24%) increase in the corpus callosum of the female offspring are biologically significant." As such, the Workgroup required evaluation of the brain morphometric measurements for the mid- and low-dose groups.

The Workgroup evaluated the brain morphometric data, including historical control data from eleven other DNT studies conducted at CTL, and found that the 24% increase in the level 4 corpus callosum thickness in PND 63 females at the high dose is not incidental (see figure below; 8/10 animals had corpus callosum thicknesses of greater than 0.39, compared to 2/10 controls). Different tissue processing schedules and machines may result in different degrees of tissue shrinkage such that data across studies may not be comparable; however, data within a single study should not be affected. Further, the concurrent controls from the clodinafop-propargyl study were found to lie within the range of historical controls from other DNT studies conducted at CTL (*i.e*, they are not aberrant). Therefore, it is appropriate to use the concurrent control data for comparison. The corpus callosum captures several major developmental processes subject to environmental insult, including myelination, axonal growth, and pruning. For example, a loss of the pruning process may result in a larger corpus callosum than is typical. Small

changes in linear morphometric measurements can reflect alterations in the development of particular brain regions that have been associated with functional deficits (Altman 1987; Rodier 1988, 1995, 2004; Rodier et al 1997). Therefore, the increased thickness of the PND 63 female corpus callosum, compared to concurrent controls, is considered biologically significant.

The registrant is required to submit corpus callosum thickness data for the mid- and low-dose male and female groups for both PNDs 12 and 63. Because the other statistically significant morphometrics findings in this study raise concern, tissues should also be examined for the mid- and low-dose groups, in both sexes, on PNDs 12 and 63 in those cases in which statistical significance was reached.

REFERENCES

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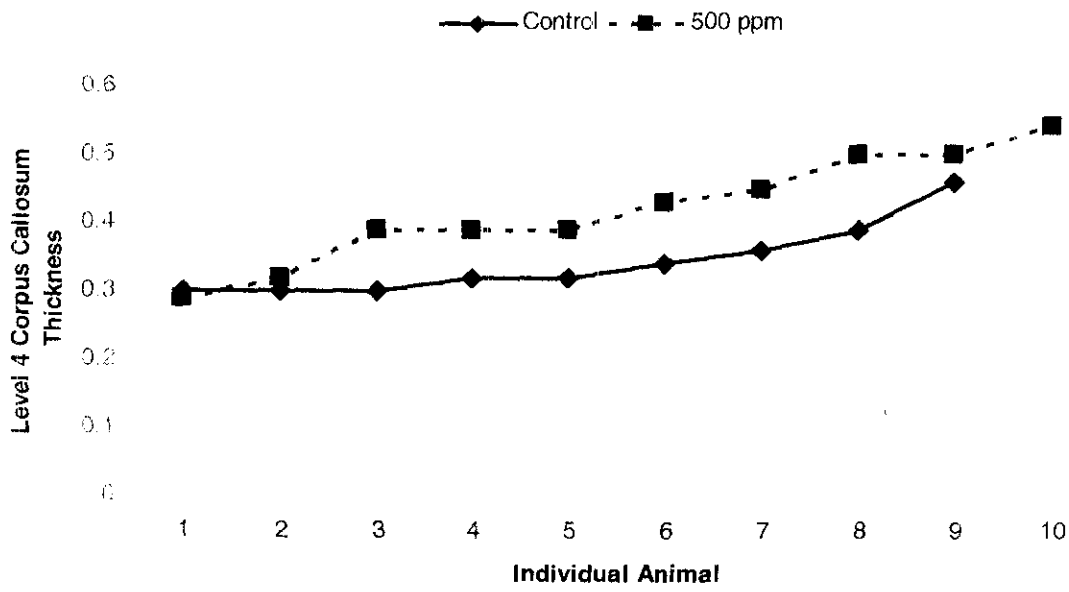
Clodinafop-Propargyl: Corpus Callosum Measurements (PND 63 Females)



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R132693

Chemical: Clodinafop-propargyl (CAS Reg. No.105512-06-9)

PC Code:
125203
HED File Code: 13000 Tox Reviews
Memo Date: 9/20/2006
File ID: TX0054358
Accession #: 412-07-0024

HED Records Reference Center
11/9/2006